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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,411	06/24/2004	Marie-Odile Galcera Contour	427.088	4397

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EXAMINER	
FREISTEIN, ANDREW B	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/500,411	GALCERA CONTOUR ET AL.	
	Examiner	Art Unit	
	Andrew B. Freistein	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-15* is/are pending in the application.

4a) Of the above claim(s) *9,10 and 13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 and 13-15 are currently pending in the instant application. Claims 11 and 12 were cancelled by preliminary amendment.

Priority

This application is a 371 of PCT/FR02/04544, filed 12/24/2002. Acknowledgement is made of Applicant's claim for foreign priority under 35 U.S.C. § 119(a)-(d), by France patent application 01/16889 filed on 12/27/2001.

Information Disclosure Statement

Applicant's information disclosure statement (IDS), filed on 06/24/2004, has been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

Restriction Requirement

In a response filed June 6, 2006, Applicant elected (with traverse) Groups I and IV, more preferably Group I. Group I is: Claims 1-8 (in part), drawn to a method of inhibiting activity comprising administering a compound of formula (I), wherein R^1 is alkyl, alkoxyalkyl, alkylthioalkyl, cycloalkyl, or (CH_2)-Z-NR^5R^6; Z is a bond or alkylene of 1 to 5 carbon atoms; R^5 is H, alkyl, aralkyl, or $(CH_2)_n$-OH, alkoxycarbonyl, haloalkoxycarbonyl, aralkoxycarbonyl; R^6 is H, alkyl, aralkyl, or $(CH_2)_n$-OH; n is 1 to 6; R^2 is H, alkyl, aralkyl; R^3 is H, alkyl, haloalkyl, alkoxy or alkylthio; R^4 is alkyl, cycloalkyl, cycloalkylalkyl, cyano, or amino; and W is S.

Applicant traverses the restriction requirement, because the PCT application was not restricted and asserts that Group I and Group IV are both directed to the same thiazole derivative.

According to MPEP 1850,

When the Markush grouping for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

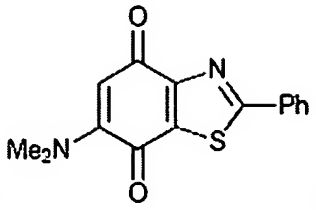
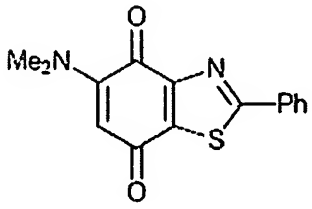
(A) All alternatives have a common property or activity; and
(B) (1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives; or
(B) (2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

In paragraph (B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity. The structural element may be a single component or a combination of individual components linked together.

In paragraph (B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

The fact that the alternatives of a Markush grouping can be differently classified should not, taken alone, be considered to be justification for a finding of a lack of unity of invention.

When dealing with alternatives, **if it can be shown that at least one Markush alternative is not novel over the prior art**, the question of unity of invention should be reconsidered by the examiner. Reconsideration does not necessarily imply that an objection of lack of unity shall be raised. (emphasis added).

In the instant application, at least one Markush alternative is not novel over the prior art. For example, Lyon et al. disclose the compounds  and  , which are claimed in the genus of claim 13 of the instant application (see Lyon et al., "Synthesis and structure verification of an analog of kuanoniamine A," J. Chem. Soc. Perkin Transactions 1: Organic and Bio-Organic Chemistry, Vol. 4, pp. 437-442 (1999); see p. 438, compounds 23a and 23b). Therefore, unity of invention was properly reconsidered.

Secondly, Groups I and IV are drawn to method of inhibition comprising distinct compounds. Namely, Group I is drawn to a method comprising a compound wherein W is a Sulfur atom and R^5 and R^6 do not form a heterocycle. On the other hand, Group IV is drawn to a method comprising a compound wherein W is an Oxygen atom and R5 and R6, together with the Nitrogen atom to which they are attached, create a heterocycle.

Consequently, restriction was proper and is made FINAL.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating human prostate cancer and human pancreatic cancer, the specification does not reasonably provide enablement for tumorous proliferative diseases, non-tumorous proliferative diseases, neurodegenerative diseases, parasitic diseases, viral infections, spontaneous alopecia, alopecia induced by exogenous products, radiation-induced alopecia, auto-immune diseases, transplant rejections, inflammatory diseases and allergies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation.

The factors include:

1. The nature of the invention;
2. The breadth of the claims;
3. The state of the prior art;
4. The relative skill of those in the art;
5. The predictability or unpredictability of the art;
6. The amount of direction or guidance presented [by the inventor];
7. The presence or absence of working examples; and
8. The quantity of experimentation necessary [to make and/or use the invention].

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

The Nature of the Invention

The instant application is drawn to compounds of Formula (I); methods of treating diseases comprising administering to a warm-blooded animal a compound of formula (I); and a method of inhibiting activity of phosphatases cdc 25 and phosphatase CD 45.

The Breadth of the Claims

Claims 1-8 are drawn to a method of inhibiting at least one activity selected from the group consisting of phosphatases cdc 25 and phosphatase CD 45 in a warm-blooded animal and a method of treating a disease selected from tumorous proliferative diseases, non-tumorous proliferative diseases, neurodegenerative diseases, parasitic diseases, viral infections, spontaneous alopecia, alopecia induced by exogenous products, radiation-induced alopecia, auto-immune diseases, transplant rejections, inflammatory diseases and allergies, comprising administering to a warm-blooded animal, a compound of formula (I).

The State of the Prior Art

The state of the art is very high in terms of finding a chemical compound that has the desired effect on the particular receptor, the bioavailability, stability, ease of production, and limited unwanted side effects.

The Cdc25 phosphatases function as key regulators of the cell during normal eukaryotic cell division and as mediators of the checkpoint response in cells with DNA damage (Kristjánsdóttir et al., "Cdc25 Phophatases and Cancer," Chemistry & Biology, Vol. 11, p. 1043-1051 (Aug. 2004)). Moreover, Cdc25 phosphatases have been shown to be effective in the treatment of specific cancers, but have not been shown to treat *all*

cancers and have not been shown to treat all of the diseases claimed in the instant application. According to Kristjánsdóttir et al., "The mechanism of Cdc25 overexpression in not clear despite numerous attempts to shed light on this important question" (p. 1047, col. 2). Further, the mechanism of Cdc25 overexpression, in most cases, in an important open problem, and its further elucidation may reveal novel anticancer targets" (p. 1048, col. 1).

The Relative Skill of Those in the Art

One of ordinary skill in the pharmaceutical arts is very high, i.e. a Ph.D. or M.D.

The Predictability or Unpredictability of the Art

The ability of treating tumorous proliferative diseases, non-tumorous proliferative diseases, neurodegenerative diseases, parasitic diseases, viral infections, spontaneous alopecia, alopecia induced by exogenous products, radiation-induced alopecia, auto-immune diseases, transplant rejections, inflammatory diseases and allergies, all with one compound or pharmaceutical composition is not known in the art. The burden of enabling one skilled in the art to treat these diseases is much greater than that of showing activity the phosphatase activity of Cdc25C recombinant enzyme, tyrosine phosphatase activity of the CD45 enzyme, and antiproliferative activity in human prostate cancer cells and human pancreas cancer cells. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of treating all of these diseases. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for treating these diseases.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified actives could actually treat all of these disease by simply administering, by any method, an amount of the claim specified compound. Furthermore, the specification fails to enable one of ordinary skill in the art to produce a chemical compound that has the required bioavailability, stability, formulation, ease of purification, hydroscopicity, recovery, etc. Thus, the specification fails to enable one of ordinary skill in the art how to make the desired compound and the method of using it in seven different ways.

The Amount of Direction or Guidance

The specification provides cellular assays showing activity the phosphatase activity of Cdc25C recombinant enzyme, tyrosine phosphatase activity of the CD45 enzyme, and antiproliferative activity in human prostate cancer cells and human pancreas cancer cells. The assays are cellular *in vitro* assays that merely provide data in a limited controlled environment. The specification does not provide any *in vivo* data nor any examples of animal testing to show how these desired compounds effect the chemokine receptor. Rather, the examples are limited to laboratory tests.

Furthermore, according to Kristjánsdóttir et al., cellular based assays have several limitations. For example, compounds that lead to G1/S and G2/M arrest, consistent with inhibition of Cdc25s, showed diminished potency (p. 1048, col. 2). Additionally, there is some discrepancy in the reported potencies of a number of Cdc25 inhibitors in vitro, which most likely from two causes: (1) Cdc25 is particularly susceptible to nonspecific inhibitors that exhibit enzyme-concentration-dependent IC-

50s; and (2) the highly reactive cysteine at the active site of the Cdc25s is particularly susceptible to covalent modification by many classes of compounds, and therefore inhibition constants will vary depending on assay conditions (p. 1049, col. 1).

The Presence or Absence of Working Examples

The specification provides no working examples of treating tumorous proliferative diseases, non-tumorous proliferative diseases, neurodegenerative diseases, parasitic diseases, viral infections, spontaneous alopecia, alopecia induced by exogenous products, radiation-induced alopecia, auto-immune diseases, transplant rejections, inflammatory diseases and allergies. The only examples provided in the specification are cellular assays.

The Quantity of Experimentation Necessary [to Make and/or Use the Invention]

The quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing caner, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue. Therefore, claims 1-8 are rejected under 35 U.S.C. § 112, 1st paragraph.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

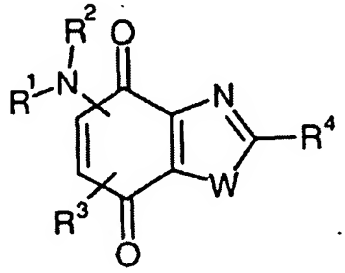
Claims 1-6 and 8 are provisionally rejected on the ground of nonstatutory double patenting over claim 14 of copending Application No. 10/562,949. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that

copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims 1-8 of the instant application is drawn to a method of:

inhibiting at least one activity selected from the group consisting of phosphatases cdc 25 and phosphatase CD 45 in a warm-blooded animals comprising administering to a warm-blooded animal in need thereof an inhibiting amount of a compound of the formula



Claims 2 and 3 are drawn to a method of treating cancer.

Determining the Scope and Content of the Copending Application

The copending application is drawn to similar compounds for treatment of cancer. Claim 14 is drawn to

A method of treating a cancer selected from the group consisting of breast cancer, lymphomas, cancers of the neck and head, lung cancer, cancer of the colon, prostate cancer and cancer of the pancreas in warm-blooded animals comprising administering to warm-blooded animals in need thereof an amount of a compound of claim 5 sufficient to treat the cancer.

The compounds of claim 5 are benzothiazole-4,7-dione compounds.

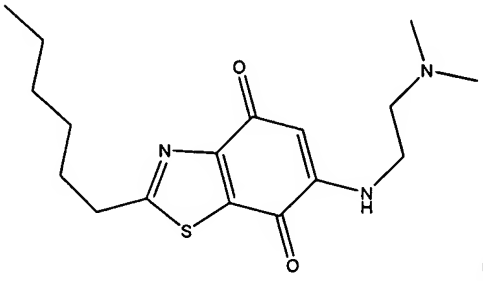
Ascertaining the Differences Between the Instant Application and the Copending Application

The instant application is drawn to a method of inhibiting activity of phosphatases for treating diseases. The diseases are tumorous proliferative diseases, non-tumorous proliferative diseases, neurodegenerative diseases, parasitic diseases, viral infections, spontaneous alopecia, alopecia induced by exogenous products, radiation-induced alopecia, auto-immune diseases, transplant rejections, inflammatory diseases and allergies.

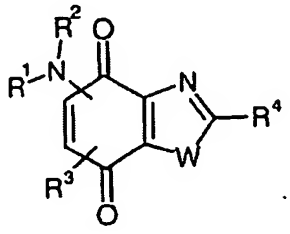
Claim 14 of the copending application is drawn to the method of treating cancers only.

Finding Prima Facie Obviousness

The genus of compounds of the instant application and the genus of compounds in the copending application overlap and both applications claim the same compounds to treat cancer. For example, claim 5 of the copending application is drawn to the compound: 6-{[2-(dimethylamino)ethyl]amino}-2-hexyl-1,3-benzothiazole-4,7-dione,



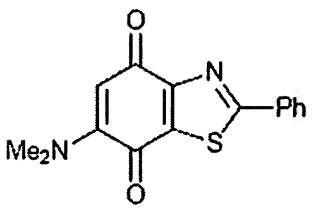
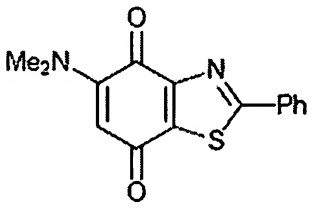
(see last species of claim 5).

The instant application claims a method of treating cancer comprising a compound of the formula (I),  , wherein R^1 is (CH_2)-Z-NR^5R^6; Z is an alkylene chain of 1-5 carbon atoms; R^5 and R^6 are each alkyl; R^2 is H; R^3 is H; and R^4 is alkyl. Thus, the compounds of the copending application are claimed for the same method of treatment in the instant application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Closest Relevant Art

The closest relevant art is: Lyon et al., "Synthesis and structure verification of an analog of kuanoniamine A," J. Chem. Soc. Perkin Transactions 1: Organic and Bio-Organic Chemistry, Vol. 4, pp. 437-442 (1999). Lyon et al. disclose the compounds  and  , which are claimed in the genus of

claim 13 of the instant application, although claim 13 is non-elected subject matter (see p. 438, compounds 23a and 23b).

The compounds disclosed in Lyon et al. do not create a 35 USC 103(a) rejection, because the reference does not provide any motivation to one of ordinary skill in the art to use the compounds.

Claim Objections

Claim 1 objected to because of the following informalities: In claim 1, in line 2, the plural "phosphatases," should be phosphatase. Similarly, in claim 1, line 3, "warm blooded animals" should be "warm blooded animal." Appropriate correction is required.

Claims 1, 4, 7 and 8 are objected to as containing non-elected subject matter.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew B. Freistein whose telephone number is (571) 272-8515. The examiner can normally be reached Monday-Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Andrew B. Freistein
Patent Examiner, AU 1626

Joseph K. McKane
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Date: June 28, 2006